REMARKS

ELECTION WITH TRAVERSE

In response to the Restriction Requirement, Applicants hereby provisionally elect, with traverse, the invention of Group I(a), claims 1-3 and 15-16 (new claims 31-33 and 37-38), directed to methods of preparing protein chains from the extracellular hemoglobin molecule of *Arenicola marina* and the proteins encoded by SEQ ID NO: 1.

CLAIM STATUS AND AMENDMENTS

Previous claims 1-30 have been cancelled and new claims 31-59 have been added. The new claims essentially correspond to the previous claims but more clearly recite the intended subject matter, correct typographical errors, and better conform to U.S. patent practice. No new matter has been added.

In Group 1(a), previous claims 1-3 and 15-16 now correspond to new claims 31-33 and 37-38, respectively. In addition, claim 53 is similar to previous claim 16, new claims 55-56 depend from claims 31 and 32 respectively, and new claims 57-58 depend from claim 53. Thus, Group 1(a) appropriately includes claims 31-33, 37-38, 53, and 55-58.

In Group 1(b), previous claims 4-6 and 17-30 correspond to claims new claims 34-36 and 39-52, respectively. Also previous claims 7-14 have been canceled but not replaced with new claims. New claim 54 is similar to previous claim 24 and new claim 59

depends from claim 52. Thus, Group 1(b) appropriately includes claims 34-36, 39-52, 54 and 59.

GROUNDS FOR TRAVERSE

The grounds for traversal are as follows.

The instant application is a 371 National stage application of PCT/FR2004/002602, and thus, PCT rules apply.

PCT Rule 13.1 requires that an international application relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (unity of invention). PCT Rule 13.2 provides that unity of invention is fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The phrase "special technical features" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The initial restriction requirement, set forth in the Office Action dated May 11, 2009, established Groups I-X. Each of Groups I-X included claims 1-30 (directed to methods of dissociating protein chains, preparing primers and preparing nucleic acid, nucleic acids and proteins encoded by the nucleic acids) but each Group was restricted to a nucleotide sequence of a particular SEQ ID NO. and its protein expression product.

In response to the initial restriction requirement, Applicants elected Group I, encompassing SEQ ID NO: 1. The Office Action now requires even further restriction between Group I(a), claims 1-3 and 15-16, directed to "chains and subunits of *Arenicola marina* hemoglobin encoded by SEQ ID NO: 1 only and methods of preparing said products," and Group I(b), claims 4-14 and 17-30, directed to "methods of preparing and using primers and methods of making cDNA encoding said hemoglobin chains or subunits."

This combination of two restriction requirements fails to comply with the PCT rules for unity of invention. Furthermore the Office Action sets forth flawed reasoning for requiring restriction in this manner.

First of all, Rule 13.2 requires a determination of unity of invention based upon defining a contribution over the prior art. The Office Action fails to follow this rule. The Office Action fails to provide any prior art reference to which such a contribution comparison can be made. For this reason alone, each of claims 1-30 (new claims 31-60) *de facto* define a contribution made over the prior art, and unity of invention exists.

Next, addressing the instant claims in more detail, claims 1-3 (new claims 31-33) are directed to methods of obtaining protein chains from the extracellular *Arenicola marina* hemoglobin molecule. The method involves bringing together a

sample of the hemoglobin molecule and a dissociation buffer and separating the protein chains from each other. The Office Action appears to have restricted the method to obtaining protein chains encoded by the nucleotide sequence of SEQ ID NO: 1 only. (The protein of SEQ ID NO: 2 is encoded by SEQ ID NO: 1).

The methods of claims 1-3 (31-33) can be applied to any of the hemoglobin molecules of *Arenicola marina* and are not limited to only those molecules comprising the protein of SEQ ID NO: 2. As detailed in the specification, for example at page 3, the extracellular hemoglobin molecules of the Annelida group are giant polymers, made up of approximately 200 polypeptide chains belonging to about 8 different types which are generally divided into two categories. The first category, comprising 144 to 192 elements, includes the "functional" polypeptide chains carrying the active site and capable of reversibly binding oxygen; these are the globin-type chains which are very similar to the α and β type chains of vertebrates. The second category, comprising 36 to 42 elements, includes the "structural" polypeptide chains that allow for the assembly of the hemoglobin polymers.

As further detailed at page 5 of the specification, the extracellular hemoglobin molecule of *Arenicola marina* typically has a mass of about 3600 kDa and is made up of 198 polypeptide chains belonging to ten different types. The methods of claims 1-3 relate to the dissociation of the extracellular hemoglobin molecule of *Arenicola marina*, making it possible to obtain each

and all of the protein chains. As further detailed at page 6 of the specification, the native hemoglobin molecule can be dissociated into subunits (e.g. monomers, dimmers, trimers, and dodecamers) under the action of non-reducing dissociating agents. After the further action of a reducing agent, the subunits can be reduced to the individual polypeptide chains.

The methods of claims 1-3 (31-33) therefore are not limited to any one specific type of polypeptide chain or one type of globulin. The methods can be generally applied to the extracellular hemoglobin molecule of *Arenicola marina* to obtain each and all of the protein chains from the molecule.

The proteins of SEQ ID NOs: 2, 4, 6, 8, 10 and 12 share a technical relationship involving the same or corresponding special technical features. Each of these proteins is an individual polypeptide chain from one hemoglobin molecule. In particular, SEQ ID NOs: 2, 4, 6, 8 and 10 relate to the globin genes A2a, A2b, A1, B2 and B1 respectively (SEQ ID NO: 12 relates to a linker gene L1).

The Office Action appears to take the position that although the globin genes are “similar,” they are only similar because they are made out of amino acids and all are proteins? The Office Action further distinguishes their similarity by comparing the hemoglobin proteins to the instances of a toxin and an enzyme having different modes of action and different structures. This position is extreme and untenable. The

polypeptide chains of at least SEQ ID NOs: 2, 4, 6, 8 and 10 (encoded by nucleic acids of SEQ ID NOs: 1, 3, 5, 7 and 9) are not just unrelated or marginally similar proteins but share the structural features of globin molecules. As globin molecules, the polypeptides include an active site capable of reversibly binding oxygen. The polypeptides and variants of each polypeptide, e.g., A2a, A2b, A1, B2 and B1, have structural and functional identity.

Furthermore, the structural features of the hemoglobin polypeptides are defined over the prior art. The prior art fails to teach or suggest the primary structure of *Arenicola marina* hemoglobin molecules, i.e., the specific amino acid sequences of SEQ ID NOs: 2, 4, 6, 8, 10 and 12. Moreover, the Office Action fails to provide any prior art reference(s) to refute that fact.

For all of these reasons, the search and examination of the methods of claims 1-3 (new claims 31-33) should be extended to the entirety of *Arenicola marina* hemoglobin molecules, and certainly to at least the polypeptides of SEQ ID NOs: 2, 4, 6, 8, 10 and 12.

Next, the remarks address claims 15 and 16 (new claims 37 and 38), directed to *Arenicola marina* hemoglobin proteins. According to the instant claims, the proteins are encoded by nucleotide sequences of nucleic acids obtained by polymerase chain reaction (PCR) utilizing specific primer pairs.

The Office Action appears to have restricted the proteins to those encoded only by the nucleotide sequence of SEQ ID NO: 1.

As detailed in the above remarks, the proteins encoded by the nucleic acids as claimed share a technical relationship involving the same or corresponding special technical features. Each of these proteins is an individual polypeptide chain from one hemoglobin molecule. In particular, at least the nucleotide sequences of SEQ ID NOs: 1, 3, 5, 7 and 9, encoding the proteins of SEQ ID NOs: 2, 4, 6, 8 and 10, relate to the globin genes A2a, A2b, A1, B2 and B1 respectively. Because the prior art fails to teach or suggest the primary structure of *Arenicola marina* hemoglobin molecules, i.e., the specific nucleotide sequences of SEQ ID NOs: 1, 3, 5, 7 and 9 and/or the specific amino acid sequences of SEQ ID NOs: 2, 4, 6, 8, 10 and 12, these proteins define a contribution over the prior art. Accordingly, unity exists between each of these proteins.

Claim 17-21 (new claims 39-43) are similar to claim 16 (38) but are directed to proteins comprising the sequence of SEQ ID NOs: 4, 6, 8, 10 and 12, respectively. Therefore, Group 1(a) should include at least new claims 39-43.

The MPEP provides that compounds are of a similar nature where: (A) all alternatives have a common property or activity; and (B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives; or (B)(2) in cases where the common structure

cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds (*see,* MPEP, 1850). In this case, the peptides of SEQ ID NOs: 2, 4, 6, 8, 10 and 12 clearly satisfy these criteria. The hemoglobin subunits and their variants have a common property and activity, have a common structure, share a significant structural element, and belong to a recognized class of compounds.

The Examples provided in Chapter 10 of the International Search and Preliminary Examination Guidelines further illustrate that unity of invention exists between the peptides of SEQ ID NOs: 2, 4, 6, 8, 10 and 12. In Example 33: Multiple Structurally and Functionally Related Polynucleotides, the claimed polynucleotides share a significant structural element and their corresponding mRNAs are expressed only in a specific cell type (hepatocytes). The polynucleotides are regarded as having the same or corresponding technical feature if the alternatives have a common property or activity, and share a significant structural element that is essential to the common property or activity. In the instant application, as detailed in the remarks above, the claimed proteins all share significant structural elements, i.e., globin variants, and share an essential common property or activity, i.e., oxygen binding, stabilization, and release. The corresponding genes are expressed only in *Arenicola*, specifically the extracellular hemoglobin. Since both of these requirements are met, the protein molecules

of SEQ ID NOs: 2, 4, 6, 8, 10 and 12 meet the requirement of unity of invention.

A second example, Example 36: Multiple Nucleic Acid Molecules Which Share Common Structure and Encode Proteins with Common Property, also illustrates how unity of invention exists in this application. This example has three nucleic acids encoding dehydrogenases that include a conserved sequence motif defining the catalytic site and dehydrogenase function of these proteins. The three nucleic acids (SEQ ID NOs: 1-3) share significant sequence homology (85-90%) at both the nucleotide and amino acid sequence levels. This example also exemplifies how the technical feature shared between the nucleic acids must define a contribution over the prior art. In the present application, however, the Office Action fails to cite any relevant prior art that could be used to show that the same or corresponding technical feature shared among the nucleic acid molecules does not define over the prior art.

For all of the reasons set forth in the remarks above, Applicants respectfully traverse the Examiner's objection for absence of a common technical feature among at least claims 15-21 (new claims 37-43). Applicants submit that the Official Action fails to satisfy the requirements of PCT Rule § 13.1 and PCT Rule § 13.2. Applicants submit that at least claims 15-21 define a contribution over the prior art and that unity of invention for at least claims 15-21 (37-43) should be recognized.

Should there be any matters that need to be resolved in the present application the Examiner is requested to contact the undersigned at the telephone number listed below.

The fee of $220.00 for the extra independent claim added is being paid online simultaneously herewith by credit card.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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